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Imaging atlas for eligibility and on-study safety of potential shoulder adverse events in anti-NGF studies (Part 3)

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SUMMARY

Despite promising results, the U.S. Food and Drug Administration (FDA) put on hold trials assessing anti-nerve growth factor (a-NGF) compounds due to concerns over accelerated rates of OA progression. The mechanism of these events is unclear but joint adverse events were observed particularly in patients using a-NGFs in combination with non-steroidal anti-inflammatory drugs (NSAIDs), suggesting that the significantly greater analgesic effect of these separate classes of drugs prompted patients to permit increased joint load without experiencing the usual pain that would limit joint stress. Development of a-NGF drugs is continuing with stringent safety criteria included in future trials as a-NGF therapies offer potential as the first new class of analgesics in many years. Potential imaging joint safety findings and exclusionary criteria for eligibility for the large weight bearing joints were presented in parts I and II of this atlas.

The shoulder as a non-weight bearing joint is likely to be less affected by increased loading due to efficacious pain reduction. However, it remains prone to degeneration especially due to concomitant rotator cuff pathology and previous trauma and inflammatory disorders. This third part of the atlas illustrates imaging findings relevant for eligibility and potential joint safety findings such as osteonecrosis, incidental findings such as large cystic lesions, inflammatory disorders, bone marrow disorders and metastases.

Introduction

Nerve growth factor (NGF) may increase the sensory nerve activity in the subchondral bone, hence offering a mechanism for both cartilage and subchondral bone as a peripheral source of pain in osteoarthritis (OA) and may offer a target for treatment by a novel class of drugs, the NGF inhibitors or a-NGFs[1]. A number of novel a-NGF monoclonal antibody agents have been tested in clinical trials for application in the treatment of pain in OA, particularly of the hip and knee[2,3].

The most clinically advanced of this class, tanezumab, is a humanized monoclonal antibody that binds and inhibits NGF and has demonstrated both good analgesic efficacy and improvement in function in a study of 450 people with knee OA[4].

Despite these initial promising successes, the U.S. Food and Drug Administration (FDA) put on hold the trials in OA due to concerns over accelerated rates of OA progression leading to osteonecrosis, accelerated loss of joint space (rapid progressive OA Type I) or rapid joint destruction and bone substance loss (rapid progressive OA Type II) leading to total joint replacement[5]. The mechanism of these events is unclear but joint adverse events were observed particularly in patients using a-NGFs in combination with non-steroidal anti-inflammatory drugs (NSAIDs), suggesting that the significantly greater analgesic effect of these separate classes of drugs prompted patients to permit increased joint load without experiencing the usual pain that would limit joint stress[1,5]. Development of a-NGF drugs is continuing with stringent safety criteria included in future trials as a-NGF therapies

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offer potential as the first new class of analgesics in many years. Potential imaging joint safety findings and exclusionary criteria for eligibility for the large weight bearing were presented in **parts I and II** of this atlas.

The shoulder as a non-weight bearing joint is likely to be less affected by increased loading due to efficacious pain reduction. However, it remains prone to degeneration especially due to concomitant rotator cuff pathology and previous trauma and inflammatory disorders. Overall shoulder OA is less prevalent than knee or hip OA with the strongest risk factor being age[6] and with osteonecrosis being a relevant contributor to subsequent shoulder OA[7].

Aim of this third part of the atlas is to illustrate imaging findings relevant for eligibility and potential joint safety findings such as osteonecrosis, incidental findings such as large cystic lesions, inflammatory disorders, bone marrow disorders and metastases.

Methods

This part of the atlas is based on eight in-person and 20+ teleconference meetings of four experienced musculoskeletal radiologists (FWR, CH, KH, AG) and a senior imaging expert (CGM) representing a contract research organization (CRO) active in a-NGF studies to define potential eligibility and safety findings relevant for a-NGF clinical trials. 250+ baseline and follow-up radiographic and Magnetic resonance imaging (MRI) image examples of shoulder joints were reviewed in consensus to define the most relevant and characteristic imaging findings of entities that may be encountered during a-NGF studies at screening or during the course of a study. Images for this atlas were derived from personal teaching and training files of these radiologists.

Results

Osteonecrosis of the shoulder is rare but may be more commonly encountered in patients with sickle cell disease with a high likelihood of progressing to humeral head collapse[8]. Incidence of humeral head involvement in an osteonecrosis patient cohort was 7% of all osteonecrosis patients, with a high incidence of concomitant or previous corticosteroid use (82%) of osteonecrosis of the hip (81%), and bilateral disease (74%)[9]. Osteonecrosis of the humeral head should be suspected in patients presenting with shoulder pain and a history of osteonecrosis in other joints[9]. Figure 1 presents early findings of humeral head osteonecrosis only visible on MRI with the humeral articular surface still preserved. Figure 2 illustrates more advanced stages of osteonecrosis with humeral articular surface collapse and marked secondary inflammatory response. Figure 3 represents findings of humeral head deformity and destruction either due to neuropathic arthropathy or hydroxyapatite formation leading to rapid progression and joint destruction, also called Milwaukee shoulder[10,11]. In addition secondary OA in osteonecrosis is visualized that include humeral head deformity and osteophyte formation. Figure 4 represents examples of anatomical variants such as glenoid dysplasia leading to OA and potential secondary inflammatory response characterized as synovitis and joint effusion on MRI. Figure 5 shows examples of post-traumatic OA and rotator cuff arthropathy leading to large osteophyte formation and humeral head migration. In addition examples of rheumatoid arthritis and chondromatosis are shown[12]. Large cystic lesions are presented in Fig. 6. Benign appearing cystic lesions are not an exclusionary diagnosis at eligibility unless they increase potential fracture risk. Figure 7 represents examples of focal and diffuse osseous malignancy that are exclusionary diagnoses at eligibility and on-study.

Fig. 1. Osteonecrosis of the shoulder. A. Anterior–posterior radiograph does not show any abnormalities. Regular articular surface contours and unremarkable humeral osseous structure is depicted. B. Sagittal proton density-weighted fat suppressed MR image exhibits focal areas of epiphyseal osteonecrosis ARCO* grade II (arrows). C. Coronal T1-weighted image of another patient shows focal subchondral area of demarcated osteonecrosis (arrows) with fat-equivalent center. D. Corresponding proton-density weighted fat suppressed image visualizes area of osteonecrosis as subchondral hyperintensity (arrows) with central hypointensity.
*ARCO (Association Research Circulation Osseous): committee on terminology and classification). ARCO News 1992; 4:41–46.

Fig. 2. Osteonecrosis of the shoulder. A. Sagittal proton density-weighted fat suppressed MRI shows post-traumatic deformity of the humeral head and well-demarcated subchondral area of osteonecrosis ARCO grade II (arrow). B. Anterior–posterior radiograph of the shoulder shows osteonecrosis ARCO grade III with humeral head surface deformity depicting subchondral collapse (arrows). C. Coronal T1-weighted MR image shows marked deformation of humeral head (arrows) and sclerosis of articulating glenoid (asterisk). Note subarticular circumscribed necrotic area of humeral head (small arrows). Finding is consistent with articular surface collapse and advanced osteonecrosis ARCO grade IV. D. Corresponding coronal T1-weighted fat suppressed contrast-enhanced image shows marked synovial activation and synovitic thickening of joint capsule (arrows). Note marked concomitant hyperintense bone marrow edema (asterisk).

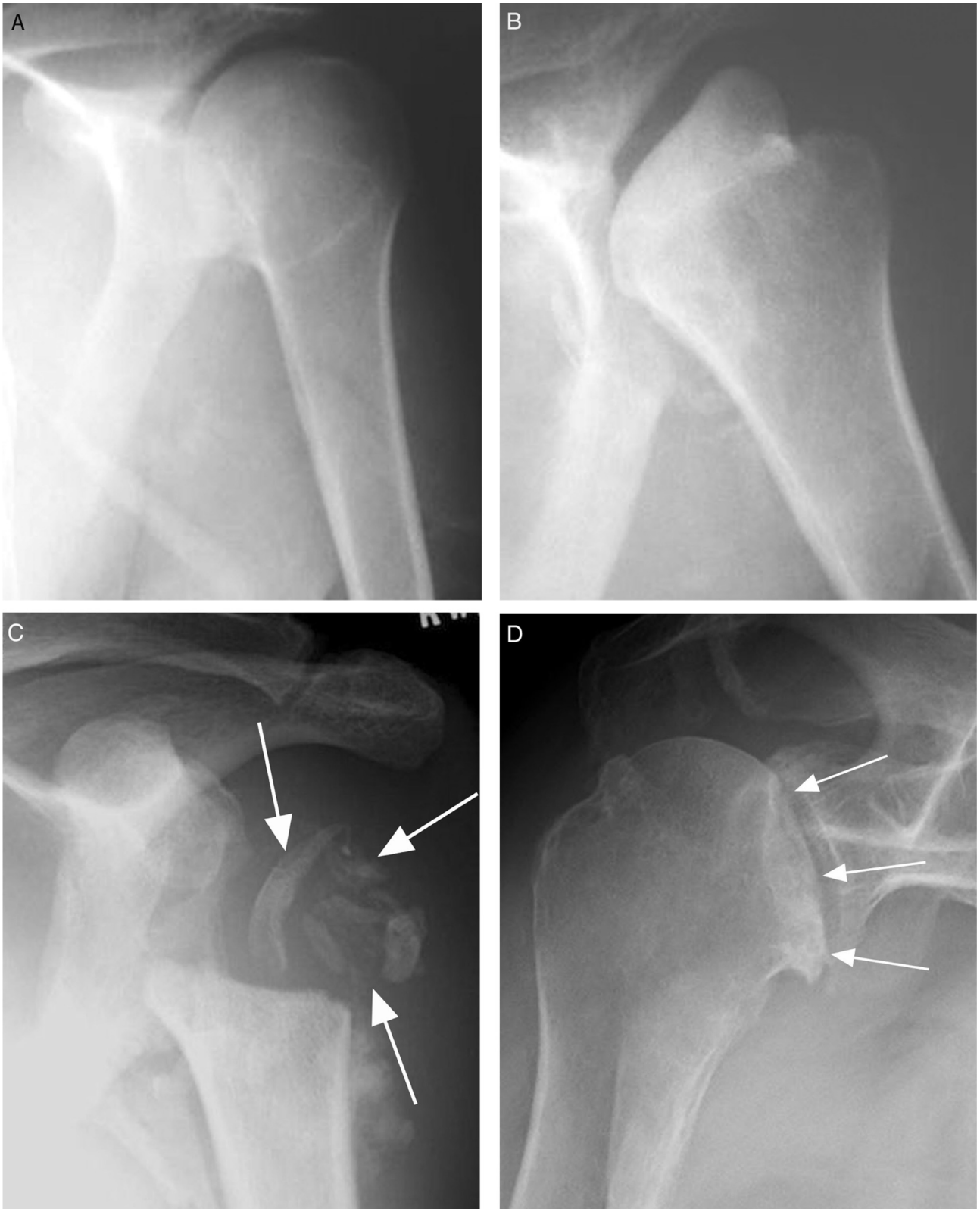

Fig. 3. Secondary joint deformity. A. Baseline radiograph shows regular articulation within the gleno-humeral joint without signs of OA. B. Same shoulder 3 months later shows marked deformity of humeral head and bone loss also of glenoid due to rapid progressive neuropathic arthropathy. C. Complete disintegration of humeral head (arrows) as a consequence of rapid destructive crystal arthropathy (hydroxyapatite – Milwaukee* shoulder). Arrows point to humeral head osseous remnants. D. Deformity of humeral head surface contour (arrows) in this gleno-humeral joint is a consequence of osteonecrosis. Note osteophyte formation at the inferior humeral head.

*McCarty DJ, Halverson PB, Carrera GF, Brewer BJ, Kozin F. "Milwaukee shoulder" – association of microspheroids containing hydroxyapatite crystals, active collagenase, and neutral protease with rotator cuff defects. I. Clinical aspects. Arthritis Rheum 1981; 24:464–473. Genta MS, Gabay C. Images in clinical medicine. Milwaukee shoulder. N Engl J Med 2006; 354:e2.

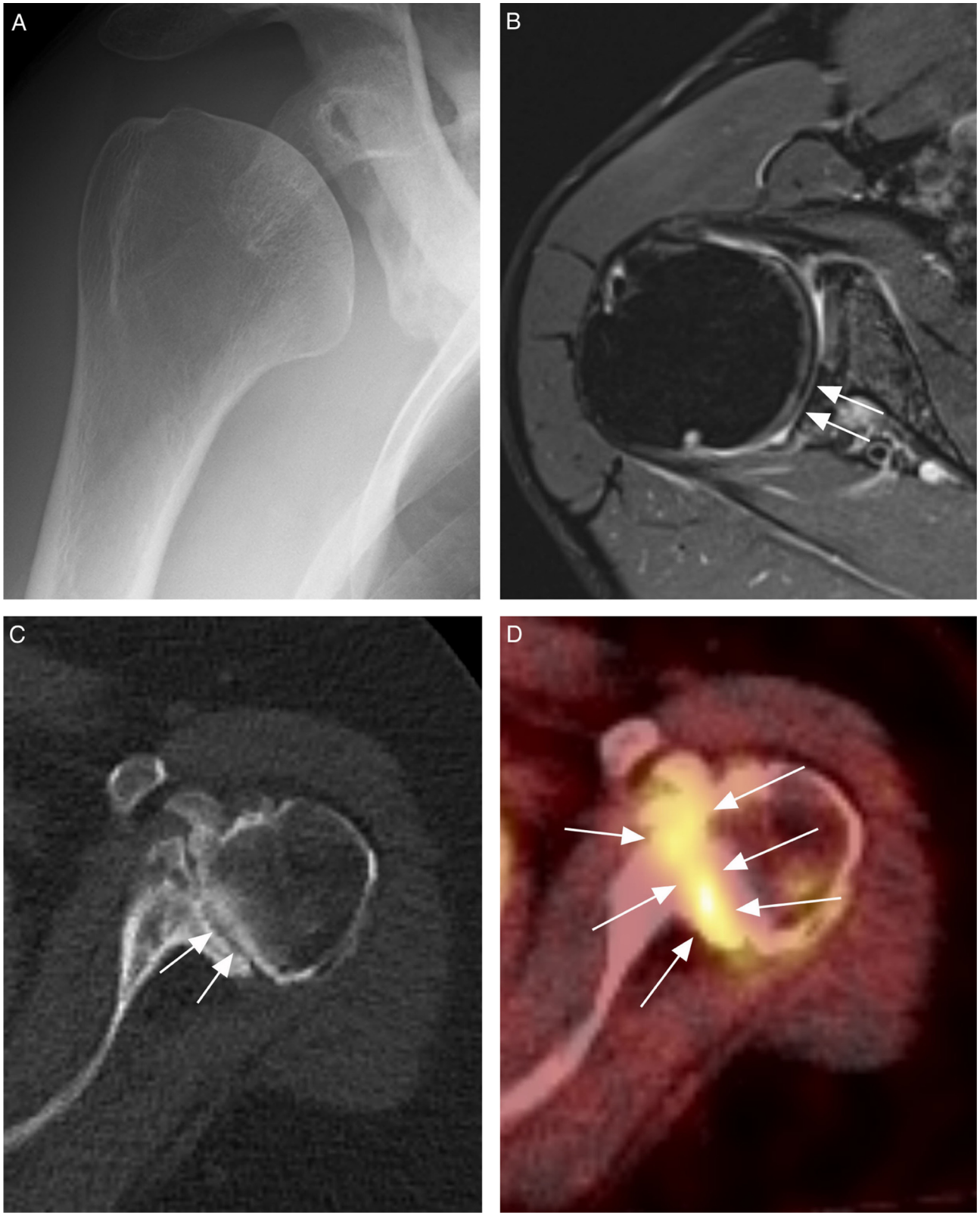

Fig. 4. Advanced OA due to anatomical variants. A. Anterior–posterior radiograph of gleno-humeral joint shows marked dysplasia of glenoid without evident signs of OA. B. Corresponding axial fat suppressed proton density-weighted MR image depicts marked cartilage loss at posterior aspect of glenoid (arrows) representing early signs of OA not revealed by radiography. C. Axial CT image of a different patient with glenoid dysplasia shows severe narrowing of joint space (arrows) and periarticular sclerosis. Note deformity of humeral head and glenoid. D. Corresponding axial fluorodeoxyglucose - positron emission tomography (FDG-PET) image depicts markedly increased glucose uptake within the joint space reflecting synovitis and explaining incident pain in this patient (arrows).

Fig. 5. Advanced OA of the shoulder. A. Post-traumatic OA characterized by large inferior humeral osteophyte (large arrows) and severe joint space narrowing (small arrows). Finding *per se* is not an adverse event but rather representing pre-existing joint damage. B. Rotator cuff arthropathy characterized by signs of OA (inferior humeral osteophyte – arrow) and cranial subluxation of humeral head due to large supraspinatus tendon tear. C. Advanced secondary OA due to rheumatoid arthritis with diffuse gleno-humeral cartilage loss and large erosive subchondral cystic alterations (arrow). Note characteristic rice-bodies and effusion in the subdeltoid bursa (asterisk). D. Synovial chondromatosis with multiple intraarticular chondroid loose bodies in the synovial cavity (arrows). In addition cartilage loss and cranialization of humeral head is shown.

Fig. 6. Cystic lesions. A. Benign cystic lesions are not a diagnosis of exclusion at eligibility if they are not considered to increase fracture risk. Coronal proton density-weighted fat suppressed image depicts glenoid ganglion cyst (thin arrows). Note incidental finding of a small full-thickness supraspinatus tendon tear (thick arrow). B. Corresponding radiograph shows lucency at the inferior glenoid (arrow). C. Another patient with a large intra-osseous benign-appearing cystic lesion depicted on this T1-weighted coronal MR image (arrows). D. Axial proton-density weighted image shows cyst as well-circumscribed hyperintense lesion (arrows). No signs of malignancy are observed.

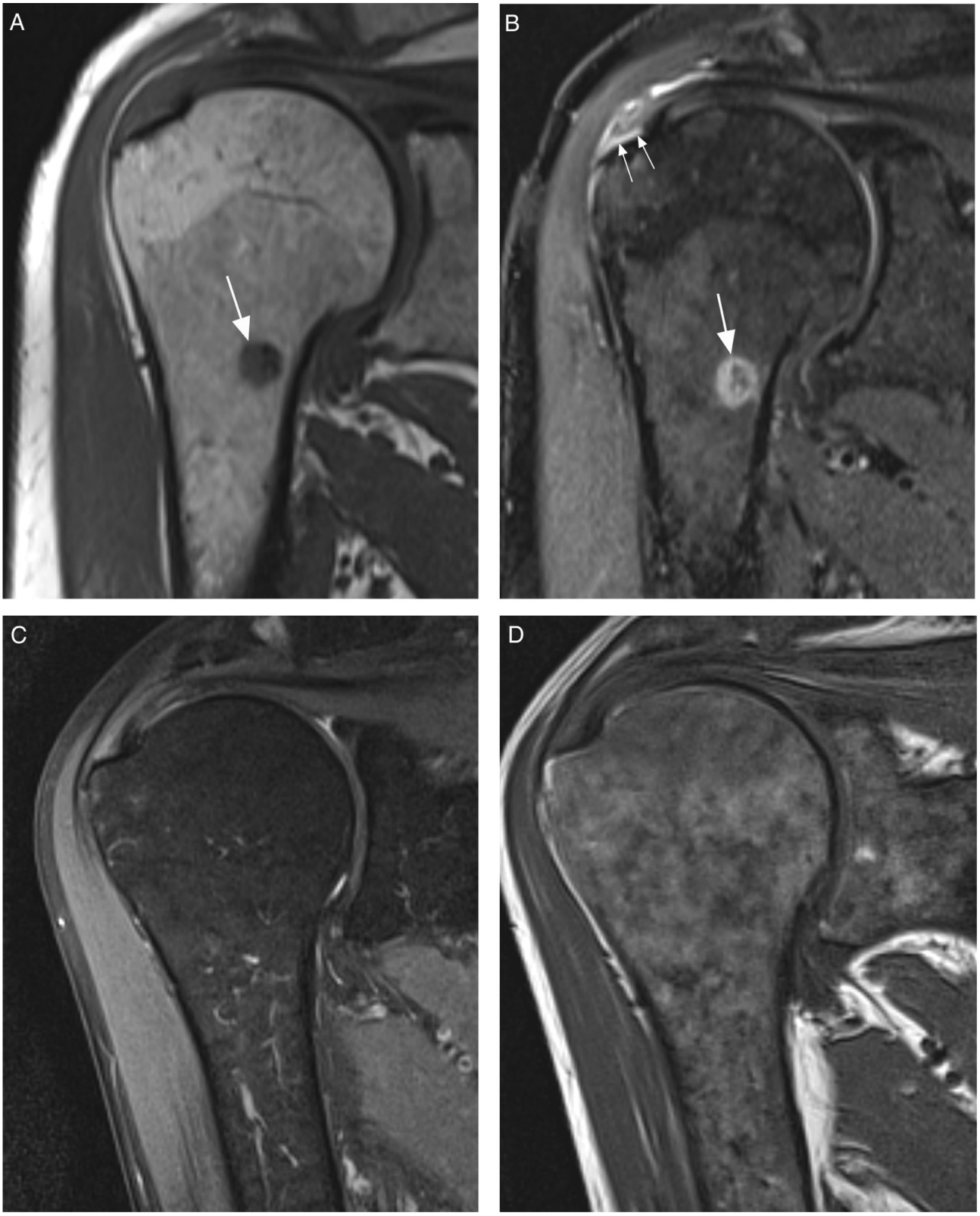

Fig. 7. Incidental osseous findings relevant for eligibility and safety but undetectable by X-ray. A. Incident painful shoulder. T1-weighted coronal MR image shows well-circumscribed hypointense lesion in the metaphyseal humeral shaft (arrow) in a patient with history of breast cancer. Finding likely not responsible for pain as there is concomitant supraspinatus tendon pathology. B. Corresponding proton density-weighted fat suppressed image depicts finding as hyperintense lesion (large arrow). Lesion is suspicious of metastasis, which was confirmed by increase in size in a short interval after 3 months. Note that there is an undersurface articular-sided partial supraspinatus tear close to the tendon attachment (small arrows). C. Normal signal intensity of bone marrow is shown on coronal fat suppressed proton-density-weighted image in this example. D. However, corresponding T1-weighted MR image exhibits marked diffuse hypointensity consistent with marrow infiltration. A diagnosis of acute lymphatic leukemia was established shortly after. Sensitivity of T1-weighted images for marrow assessment is exemplified in this image.

Authors contributions

(1) All authors were involved in the conception and design of the study, or acquisition of data, or analysis and interpretation of data.
(2) All authors contributed to drafting the article or revising it critically for important intellectual content.
(3) All authors gave their final approval of the manuscript to be submitted.

Additional contributions

- Analysis and interpretation of the data: FWR, CWH, CGM, KH, AG
- Drafting of the article: FWR, CWH, CGM, KH, AG
- Provision of study materials or patients: FWR, CWH, CGM, KH, AG
- Statistical expertise: N/A
- Obtaining of funding: FWR, CGM, AG
- Collection and assembly of data: FWR, CWH, CGM, KH, AG

Responsibility for the integrity of the work as a whole, from inception to finished article, is taken by F Roemer, MD (first author; froemer@bu.edu).

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Competing interests

Dr Guermazi has received consultancies, speaking fees, and/or honoraria from Sanofi-Aventis, Merck Serono, and TissuGene and is President and shareholder of Boston Imaging Core Lab (BICL), LLC a company providing image assessment services. Dr Roemer is Chief Medical Officer, Director of Research and shareholder of BICL, LLC. Dr Colin Miller is a full time employee of BioClinica. Dr Curtis Hayes and Dr Kevin Hoover are consultants to BioClinica.

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